REMARKS

Pending Claims 152 and 153 have been amended to change the term "polypeptide" to "moiety", for correct antecedent basis since biotin and iminobiotin are not polypeptides.

New Claims 158 and 159 are dependent on pending Claim 101 and are directed to compositions containing compounds in which the linkage group contains a primary amine (claim 158), or an allylamine or an allyl-(3-amino-2-hydroxy-1-propyl) ether (NAGE) (claim 159). Support for the various reactive terminal groups is found, for example, at page 13, line 10 to page 14, line 5 and at page 15, lines 12 -17 of the specification.

New Claim 160 is dependent on Claim 156 and is directed to a composition in which moiety A (which comprises an indicator molecule) is an allylamine group linked directly to moiety B (i.e., a purine, deazapurine or pyrimidine). New Claim 161 is dependent on Claim 156 and is directed to a composition in which moiety A (which comprises an indicator molecule) contains an olefinic (i.e., a C=C) bond. Support for New Claims 160 and 161 is found, for example, on p. 20, lns. 15-20 of the specification.

Pending Claim 148 has been amended to delete references to biotin and iminobiotin from the Markush group describing the ligand of Claims 101 or 110. These references to biotin and iminobiotin have been added to the Markush group describing the ligand of Claims 101 or 110 in New Claim 162. New Claim 162 also contains a cofactor as a member of the Markush group describing the ligand. Support for a cofactor ligand is found, for example, on p.4, ln. 4 and p. 12, lns. 25-30, right column, in the listing

of lipoic acid as a ligand. Lipoic acid is a cofactor of a number of enzymes.

New claim 163 is dependent on Claim 148 and is directed to a composition in which the hapten is dinitrophenol (DNP). Support for the hapten DNP is found on p. 16, lns. 1-15.

Enablement

Applicants also wish to further expand on their previous arguments in the response dated August 26, 1992 in parent application 07/130,097 concerning the rejection of claims 101-103, 110-112, 138-139 and 146-151 and the objection to the specification under 35 U.S.C. § 112, first paragraph as "failing to provide an enabling disclosure". Applicants wish to refer the Examiner to a number of references which are already of record in the parent application (see the Information Disclosure Statement and accompanying PTO-1449 form filed August 4, 1989 in parent application 07/130,097) and a newly cited reference: Lee et al., "8-(6-Aminohexyl)-Amino-Adenine Nucleotide Derivatives for Affinity Chromatography", Arch. Bioch. Biophys. 163:561-569 (1974).

In the parent application 07/130,097, the Examiner asserted that there are no embodiments in the instant specification which describe how the attachment of labels to the 8-position of purines or to the 7-position of a deazapurine is to be accomplished. The Examiner also asserted that there are no specific embodiments of either the 2',3'- or 3',5'-cyclic monophosphates.

Enablement of labeling at the 8-position of a purine

With respect to the enablement of attaching a label to the 8-position of a purine, Applicants reiterate that the specification need not detail the specifics of this reaction since it was well known in the art how to attach a linker arm to the 8-position of a purine at the time of filing of the application from which this application claims its priority. Applicants draw the Examiner's attention to Lee et al., "8-(6-Aminohexyl)-Amino-Adenine Nucleotide Derivatives for Affinity Chromatography", Arch. Bioch. Biophys. 163:561-569 (1974) (newly cited) which discloses a method of attaching a (6-aminohexyl) amino group (a linker with a reactive terminal group) to the 8-position of adenosine monophosphate (a purine). See especially p. 562, col. 2. Given the teaching of Applicants' specification that a detectable moiety, such as biotin, can be attached to a nucleotide base via a linker having a reactive terminal group, one of ordinary skill in the art would find it a routine exercise to apply this teaching to the 8-(6-aminohexyl) amino adenosine phosphate described by Lee et al. In fact, PCT application WO-83/02276 (of record in the parent application) discloses that this method of attaching a label to the 8-position of a purine is indeed successful. See p.11, lns. 4-11. Furthermore, PCT application WO-83/02277 (of record in the parent application) discloses that such 8-labeled purines can be incorporated into polynucleotides. See p. 13.

Enablement of labeling at the 7-position of a deazapurine

With respect to the attachment of a label to the 7-position of a deazapurine, Applicants submit that the specification need not detail the specifics of this reaction since

the method of attachment of a linker arm to the 7-position of a deazapurine would have been obvious to one skilled in the art at the time of filing of the application from which this application claims its priority, given the teachings of the specification. For example, Dale et al., Proc. Natl. Acad. Sci. USA 70:2238 (1973) (of record in the parent application), demonstrates that the chemistry used to mercurate a pyrimidine at the 5-position (which permits the addition of a linker as described in the specification) would similarly mercurate a deazapurine at the 7-position. Thus, given the teachings of the specification concerning how to mercurate the 5-position of a pyrimidine to allow the attachment of a linker arm and label, and the prior art teachings of Dale et al. that the 7-position of a deazapurine can be mercurated in the same way using the same conditions, one of ordinary skill in the art would have known how to attach a label at the 7-position of deazapurine at the time of filing of the application from which this application claims priority.

Enablement of labeling of 3',5'-cyclic monophosphates

With respect to the rejection of claims 138 and 139 under 35 U.S.C. § 112, first and second paragraphs, because 2',3'- and 3',5'-cyclic monophosphates are allegedly not represented by a specific embodiment, Applicants reiterate that a disclosure of a specific embodiment for the currently claimed 3',5'-cyclic monophosphates is not necessary. (Claim 139, directed to compounds containing 2',3'-cyclic monophosphates, was canceled without prejudice in the Amendment after final dated August 27, 1991 and therefore renders the rejection of that claim moot). The following references (all of record in the parent application) demonstrate that nucleotides containing such cyclic phosphates are

functionally similar to nucleotides in which the phosphates are not cyclized, that these cyclic phosphates can be functionalized at the 8-position and furthermore, that this was known to one of skill in the art. For example, Shuman et al., U.S. Patent No. 3,915,958, "6-substituted purine nucleotides" discloses a process for preparing 8-bromoadenosine 3',5'-cyclic phosphate-N^1-oxide. See example 1. Christensen et al., U.S. Patent No. 3,968,101, "8-substituted cyclic nucleotides by free radical alkylation and acylation" discloses a method for introducing alkyl and acyl groups directly onto the 8-position of existing guanosine 3',5'-cyclic phosphate molecules (see columns 3-4) and also disclose a $-NH_2$ reactive group at the end of the substitutent (see structures 15 and 16 in column 6). Christensen et al. also cite articles disclosing the synthesis of a number of 8-alkylthio-, 8-arylthio- and 8-alkylamino-cGMP derivatives, along with 8-hydroxy- and 8-bromo-cGMP (see column 2, lines 60-70). Finally, Yokota et al., U.S. Patent No. 4,048,307, "Cyclic adenosine monophosphate 8-substituted derivatives" (issued Sept. 13, 1977) discloses cyclic adenosine monophosphate derivatives containing alkyl substituents added to the 8-position of 3',5' cyclic-monophosphate. Yokota et al. also states that other 8-substituted c-AMP derivatives, such as alkylamino or alkylthio derivatives, were known in the art. See col. 2, lns. 22-33. Thus, Applicants reiterate, it would have been routine for one of ordinary skill in the art to substitute cyclic phosphates in the modified nucleotides and oligonucleotides of the invention or to attach a linker to a nucleotide containing a 3',5'-cyclic monophosphate as suggested in the specification, given the teaching of the specification regarding non-cyclized phosphates and the prior art disclosures regarding functionalized cyclic phosphates.

Information Disclosure Statement

Applicants wish to make of record in this application the documents cited in the Information Disclosure Statement and Supplemental Information Disclosure Statement filed on August 4, 1989 and October 7, 1991, respectively. Applicants also wish to make of record two additional references, (1) Lee et al., "8-(6-Aminohexyl)-Amino-Adenine Nucleotide Derivatives for Affinity Chromatography", Arch. Bioch. Biophys. 163:561-569 (1974) and (2) Kourilsky et al., "Method of Detecting and Characterizing a Nucleic Acid or Reactant for the Application of this Method", U.S. Patent No. 4,581,333, issued April 8, 1986; priority date April 13, 1978 (France).

An updated Information Disclosure Statement and PTO-1449 form compiling all the references cited to date are attached.

CONCLUSION

After entering the Amendments after Final dated August 26, 1991 and August 27, 1991 and new Claims 158-162 in the present Preliminary Amendment, Claims 102-103, 110-112, 138, 148 and 152-163 will be pending in the application. These claims are presented for further examination.

In view of the amendments to the claims and discussion of the issues in the above-referenced amendments, a determination that all of the claims now pending are in condition for allowance is earnestly submitted. Allowance of applicants' pending claims is respectfully requested.

Respectfully submitted,

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